UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,265	08/31/2001	Timothy A. Springer	CBN-002CP	1985

26161 7590 04/07/2005

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,265	SPRINGER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-26, 30, 74, 76-80, 83-84, 87-88, 105-106, 110, 112-117, 122-129 and 131-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/24/05& 2/16/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

Continuation of Disposition of Claims: Claims pending in the application are 25,26,30,74,76-80,83,84,87,88,105,106,110,112-117,122-129 and 131-134.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/24/05 has been entered.

2. Claims 25-26, 30, 74, 76-80, 83-84, 87-88, 105-106, 110, 112-117, 122-129 and 131-134 are pending and under examination in the instant application.

3. Applicant's IDS, filed 1/24/05 and 2/16/05, is acknowledged.

4. This application contains an abstract in impropriate format because the abstract contains two paragraphs.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

6. Claims 26, 74, 84, 87-88, 110, 112-117, 122-126, 128-129, 131-134 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The "I-domain" recited in claims 74 and 79 has no antecedent basis in base claim 25. Base claim 25 only recites the open conformer.

B. The "E284C/E301C" recited in claim 87 and the"K287C/K294C" recited in claim 88 have no antecedent basis in base claim 84. Base claim 84 recites only "E284C-E301C or K287C-K294C"

C. The "E284C-E301C" or "K287C-K294C" mutations recited in claims 26, 84, 131-134 are ambiguous because it is unclear whether the "-" indicates amino acids from position E284C to position E301C for example, or the mutations are specific to those positions only within the αL integrin.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 25-26, 74, 76-80, 83, 105-106, 110, 112-117, 122-129 and 131-132 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or an antigen binding fragment thereof, which specifically binds to a modified integrin I-domain in the open conformation comprises substitutions E284/E301C or K287C/K294C in an αL subunit but not to a modified integrin I-domain in the closed conformation by the substitutions of K289C/K294C or a recombinant anti-integrin antibody, or an antigen binding fragment thereof, which specifically binds to the open conformation of an αL integrin I-domain relative to the closed conformer of an αL integrin I-domain, and inhibits interaction of LFA-1 integrin and a cognate LFA-1 ligand, does not reasonably provide enablement for an antibody or an antigen binding fragment thereof which specifically binds to a recombinant antibody, or an antigen binding fragment thereof, which specifically binds to the "open conformer" αL integrin relative to "another conformer" and in claim 25, or an antibody or an antigen binding fragment thereof, which binds to an activation specific epitope on an integrin I-domain of αL in the open conformation defined by the "E284C-E301C" or "K287C-K294C" mutations in claim 26, or a recombinant anti-integrin antibody, or an antigen binding fragment thereof, which specifically binds to the open conformer of an αL integrin I-domain relative to the closed conformer of an αL integrin I-domain, and inhibits interaction of LFA-1 integrin and a cognate LFA-1 integrin Ligand in claim 70, wherein said antibody comprises any "portion " of a human antibody and any "portion" or a non-human antibody in claim 76, an antibody or an antigen binding fragment thereof, which binds to an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation in claim 83, the antibody further comprising a therapeutic moiety in claim 117, wherein the therapeutic moiety comprises a cytotoxin in claim 117, a radioactive metal ion in lciam 123, a protein possessing a "desired biological activity" in claim

125, a toxin in claim 126, a pharmaceutical composition thereof in claims 127-129, wherein the open conformer is defined by the "E284-E301C or K287-K294C" mutations in claims 131-132, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Besides the antibody or an antigen binding fragment thereof, which specifically binds to a modified integrin I-domain in the open conformation comprises substitutions E284/E301C or K287C/K294C in an αL subunit but not to a modified integrin I-domain in the closed conformation by the substitutions of K289C/K294C, the specification fails to provide sufficient guidance and direction as to make and use antibodies that binds the "open conformer" of αL relative to "another" conformer, or binds to activation specific epitope on an integrin I-domain of αL in the open conformation defined by the "E284C-E301C" or "K287C-K294C" mutations, or binds to any "open conformer" but not to any closed conformer.

Applicant is relying upon a single species to support an entire genus. The claims as written encompass a broad genus of antibodies with an unlimited number of possibilities with regard to the source and type of molecule that contains the I-domain and the conformation status of the I-domain. Dr. Cohen's Declaration provides only one species of an antibody (IgG#57) that binds to the I-domain in the open conformation (K287C/294C) in the αL subunit, but not to the I-domain in the closed conformation by the substitutions K289C/K294C) in the αL subunit, yet Applicant claims an antibody that binds any "open" conformer/conformation of αL (i.e., from human, mouse, rat, among others). It is noted that the specification on page 67, last paragraph discloses that the monoclonal antibodies BL5, F8.8, CBRLFA-1/9, May.03, TS1/22 and TS2/6 strongly inhibited binding of both wild type and mutant K287C/K294C, and the levels of inhibition to wild type LFA-1 and the mutant were similar. Further the specification discloses that monoclonal antibodies TS1/11 and TS1/12 inhibited >90% binding of transfectants that express wild type LFA1, these antibodies showed reduced inhibition on binding of mutant K287C/D294C (40-60%). Furthermore, monoclonal antibodies TS2/14, 25-3-1 and CBRLFA-1/1 show >90% inhibition on binding of wild type but had no to little inhibition on mutant K287C/K294C binding to ICAM-1. Finally, Table 3 in the specification at page 69, provides no single example of an antibody that binds the open conformation but not the closed conformation of the LFA-1. In the contrary Table 3, provides antibody that binds either to both closed and opened conformation or to the closed conformation but not to the opened conformation. It is not clear how one of skill would make an antibody to any integrin in the open conformation (whether it is chemically modified or naturally activated) other than an antibody directed to the specific open conformation mutations E284/E301C or K287C/K294C in the αL subunit I-domain and tested with the with the specific closed conformation mutation K289C/K294C in the αL subunit I-domain to indicate that the resultant antibody does not bind to the closed conformation. Without some kind of substantive structure of an I-domain in the open conformation, it would require undue experimentation for one of skill to make antibodies to that would bind to the open conformation but not to the closed conformation encompassed by the instant claims.

Claim 76, recites an antibody comprises a portion of a human antibody and a portion of a non-human antibody. However, one of ordinary skill in the art would not know what portion is derive form a human and what portion derived form a non-human. Further, a combination of any human and non-human portions would not result in a functional antibody or an antibody that specifically binds to a modified integrin I-domain. For example, a framework region form a human and a framework form non-human for example would not result in a functional antibody. A constant domain from a human and a constant domain form non-human also would not result in a functional antibody. A combination of a framework (whether it is a human or non-human) and a constant domain (whether it is a human or non-human) would not result in a functional antibody.

Claims 117-124 recite that the antibody is linked to a therapeutic moiety. The exemplification in the specification is drawn to inhibition of LFA-1 function *in vitro* and *in vivo* by soluble I-domain mutants. While the specification uses "active immunization" with soluble open I-domain to block the firm adhesion of T-lymphocytes to high endothelial venules, which is LFA-1 dependent (see example 5 in particular), the claims requires a "passive immunization" with an antibody to a specific conformation of the I-domain of αL. Such assay may provide an indication that particular compounds/compositions are appropriate to target for *further experimental consideration*. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from *these* assays to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

Applicant's arguments, filed 1/24/05, have been fully considered, but have not been found convincing.

In view of Applicant's persuasive arguments, with respect to the pharmaceutical composition and the evidence that that U.S. Patent 5,622,700 teaches therapeutic methods for using a conventional anti-LFA-1 antibody, the rejection with respect to the enablement of the pharmaceutical composition of the claimed antibodies are hereby withdrawn.

Applicant submits that the specification does teach how to make an integrin in the open conformation and provides a number of examples of modification of integrins in the open conformation. Applicant directs the Examiner's attention to the specification on page 15, lines 27-30 of the specification which discloses a number of αL mutations that are stabilized in the open conformation. The Examiner agrees with applicant's assertion and enabled the specification for the a recombinant anti-integrin antibody, or an antigen binding fragment thereof, which specifically binds to the open conformation of an αL integrin I-domain relative to the closed conformer of an αL integrin I-domain, and inhibits interaction of LFA-1 integrin and a cognate LFA-1 ligand.

Regarding, the term "specifically binds", Applicant asserts that the term "specific binding," as used in this application, is relative to some remote protein not mentioned in the specification or

relative to an integrin in a different conformation. However, applicant argues that in any circumstance, the term "specific binding" is relative, Applicant provides examples wherein specific binding of an antibody to an HIV-1 coat protein might mean that the antibody can distinguish a viral HIV protein fro a human cellular protein, or that the antibody can distinguish between an HIV protein and a herpes virus protein, or that the antibody can distinguish an HIV-1 protein from an HIV-2 protein. Applicant submits that all these interpretations are consistent with the art known meaning of the term "specific binding." Applicant submits that context is required to resolve the appropriate meaning. Applicant contends that the Examiner did not give sufficient weight to the specification in construing the term. Applicant argues in conjunction with case law (AstraZeneca) that the applicants have clearly and repeatedly use the term "selective binding" or "specific binding" to refer to binding to one particular conformation, i.e., one conformation rather than another. The Applicant points to the specification on pages 12, lines 27-31 and page 4, lines 17-14. Applicant contends that the terms "specific binding" and "selective binding" throughout the specification provide a clear lexicography which defines these terms to mean specificity for one conformer relative to another. Further, Applicant argues that the usage of these terms in the specification requires a degree of preference that is more pronounced than the negligible preferences of antibodies that are described in the specification as binding "equally well" to open and closed conformation I-domains. Applicant further submits that the specification indicates that a difference in the range of 0-18% for binding to the open versus the closed conformation I-domains does not amount to specific binding, whereas a difference of about 50% or greater does amount to specific binding. Applicant concluded that antibodies that specifically bind to the open conformer of an I-domain that requires experimentally significant degree of preferential binding to the open conformation relative to the closed conformation.

The Examiner cannot see any difference between the art-recognized specificity of an antibody and Applicant's usage of the term. As in the art-recognized specificity, the specification defined the specificity in a way that the claimed antibody can recognized both conformational forms of the αL integrin subunit. While applicant is trying to provide a preference that the claimed antibody binds to the open conformation relative to the closed conformation, that meaning does not preclude that the same antibody "cross react"/"equally binding" with the closed conformation.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 26, 83, 105, 110 and 112-113 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997) (of record), as is evidenced by Lu *et al* (Proc Natl Acad Sci 98:2393-2398, 2002) (of record) and the specification on page 76, lines 7-8 and page 77, Table 6.

Huang *et al* teach five mAb antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which specifically bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin αL subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the specific antibodies bind to an activation specific epitope on an integrin I-domain of αL in the open conformation defined by the E284C-E301C or K287C-K294C mutations, and inhibits interaction of LFA-1 integrin and a cognate LFA-1 integrin ligand claimed in claim 26, the antibodies to an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation claimed in claim 83, These limitations are considered an inherent property of the reference antibodies.

As is evidenced by Lu *et al*, that antibodies against αL I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of αL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of αL subunit of LFA-1 (page 2395, Table 2 in particular). Lu *et al* compare the binding of modified integrin I-domain in the open conformation (K287C/K294C) relative to the modified integrin I-domain in the closed conformation (L289C/K294C) as well as (see table 1 in particular) the wild type. The binding to the open and closed conformation mutants is almost equivalent among the antibodies or differs by only a few percentage points.

Further, as is evidenced by the specification on page 76, lines 7-8 and page 77, Table 6 that the affinity of E284C/E301C mutant is nearly comparable to K287C/K294C mutant affinity (e.g. predicted open conformation binds with high affinity).

Claims 112-113 are included because the referenced antibody would inherently inhibit the interaction of LFA-1 integrin and ICAM-1, ICAM-2 or ICAM-3 since the claimed antibody are the same as the referenced antibody.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to an activation specific epitope on an integrin I-domain of αL in the open conformation defined b the E284C-E301C or K287C-K294C mutations, and inhibits interaction of LFA-1 integrin and a cognate LFA-1 integrin ligand or bind to an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 128-129 are rejected under 35 U.S.C. 103(a) as being obvious over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S Patent No. 6,413,963 (of record).

The teachings of Huang *et al* and Lu *et al* cited and the specification both as an evidentiary reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition and a pharmaceutically acceptable carrier.

The `963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The `963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antibodies taught by Huang *et al* reference in a pharmaceutical compositions in a pharmaceutically acceptable carrier taught by the `963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 114-117 and 122-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 6,572,856.

The teachings of Huang *et al,* Lu *et al* and the specification both cited as an evidentiary reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the antibody further comprising a physically linked detectable substance in claim 114, wherein the physically linked detectable substance comprises and enzyme, a fluorescenct material, or a radioactive material in claims 115-116, or the antibody further comprising a therapeutic moiety in claims 117-121, wherein the therapeutic moiety comprises a cytotoxin in claim 122, a chemical therapeutic agent in claim 124, a protein possessing a desired biological activity in claim 125, a toxin in claim 126.

The `856 patent teaches monoclonal antibodies immunospecific for C3b(i) are conjugated to a therapeutic moiety such as a chemotherapeutic cytotoxin, e.g., a cytostatic or cytocidal agent (e.g., paclitaxol, cytochalasin B or diphtheria toxin), a thrombotic or anti-angiogenic agent or a radioactive label. In another embodiment, monoclonal antibodies immunospecific for C3b(i) are conjugated to a detectable substrate such as, e.g., an enzyme, fluorescent marker, luminescent material, bioluminescent material, or radioactive material (see col. 8 lines 45 to col. 9, line 8 in particular). Further, an antibody or fragment thereof can be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide. Therapeutic agents include antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), (e.g., vincristine and vinblastine). (see column 28, lines 15-38 in particular) the `856 patent teaches that the drug moiety can be a protein or polypeptide possessing a desired biological activity such as toxin (see col., 28, lines 51-55). The `856 patent further teaches that the anti-C3b(i) antibodies or fragments thereof are conjugated to a diagnostic or therapeutic agent can bed used diagnostically as a part of a clinical testing procedure to determine the efficacy of a given treatment regimen (see col., 27, lines 57-61 in particular). Finally, the `856 patent teaches that the antibodies specific for C3b(i) can be utilized to target tumor cells for the delivery of therapeutic or diagnostic agents, including cytotoxic, chemotherapeutic, immune-enhancing drugs, radioactive compounds, genetic material and immune effector cells (see col., 45, lines 1-5 in particular)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the antibodies and fragments thereof, which specifically bind to an integrin I-domain taught by Huang *et al* with a physically linked detectable substance, wherein the

physically linked detectable substance comprises and enzyme, a fluorescenct material, or a radioactive material, or a therapeutic moiety, wherein the therapeutic moiety comprises a cytotoxin, a chemical therapeutic agent, a protein possessing a desired biological activity, a toxin taught by the `856 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such antibodies or fragments thereof which are conjugated to a diagnostic or therapeutic agent can bed used diagnostically as a part of a clinical testing procedure to determine the efficacy of a given treatment regimen. Further, such conjugated antibodies can be utilized to target tumor cells for the delivery of therapeutic or diagnostic agents, including cytotoxic, chemotherapeutic, immune-enhancing drugs, radioactive compounds, genetic material and immune effector cells as taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant did not address this rejection of record in the reply submitted 1/24/05.

15. Claims 25, 30, 74, 76-80, 110, 112-113 and 131-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 5,843,712 (of record).

Huang *et al* teach five monoclonal antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which specifically bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin αL subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the specific antibodies bind to a modified I-domain of αL subunit containing amino acid substitutions E284C/E301C, wherein the modified integrin polypeptide is stabilized in the open conformation. These limitations are considered an inherent property of the reference antibodies. Huang et al further teaches that LFA-1 binds three cell surface ligands that are members of the Ig superfamily, intercellular adhesion molecule (ICAM)-1, ICAM-2, and ICAM-3 (see page 3162, introduction 1st ¶ in particular). Further, Huang et al teach that the antibodies in solution, (2μg of purified IgG or 2μlo of ascites) were added to 200μl (1% Triton X-100/150mM NaCl/20 mM Tris.HCl, pH 7.5) of the precleared supernatants (see page 3163, 2nd col., 2nd ¶ in particular).

As is evidenced by Lu *et al*, that antibodies against αL I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of αL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of αL subunit of LFA-1 (page 2395, Table 2 in particular). Lu *et al*

compare the binding of modified integrin I-domain in the open conformation (K287C/K294C) relative to the modified integrin I-domain in the closed conformation (L289C/K294C) as well as (see table 1 in particular) the wild type. The binding to the open and closed conformation mutants is almost equivalent among the antibodies or differs by only a few percentage points.

Further, as is evidenced by the specification on page 76, lines 7-8 and page 77, Table 6 that the affinity of E284C/E301C mutant is nearly comparable to K287C/K294C mutant affinity (e.g. predicted open conformation binds with high affinity).

The claimed invention differs from the reference teachings only by the recitation of a recombinant antibody, the antibody comprises a portion of human antibody and a portion of a non-human antibody in claim 76, a humanized antibody in claim 77, and a chimeric antibody in claim 78.

The `712 patent teaches that the expression of recombinant antibodies in mammalian cells offers great advantages with respect to post-translational modifications, stability, immunogenicity, and yields (see column 1, lines 40-45 in particular), wherein Sindbis virus vectors offer a powerful tool for the rapid production of genetically engineered antibodies (column 1m lines 1, lines 48-56 in particular). The `712 patent further teaches that the Sindbis virus vector system can be useful to produce recombinant antibodies that replace immunoglobulin therapies that are presently being used in the treatment of certain inflammatory disorders, immunodeficiency states, and viral infections. The advantages of such recombinant antibodies (versus serum immunoglobulin therapy MAbs derived from mouse hybridoma cells) would be that they can easily be humanized. Further these antibodies can be custom designed to modify their specificity, and produced in very large quantities (see column 16, lines 8-16 in particular). Finally, the `712 patent teaches that the Sindbis virus vector system can easily be adapted to produce chimeric, humanized or human antibodies. The feasibility of producing high yields of humanized biologically active antibodies suggests that the Sindbis virus vector system can be useful for the generation of therapeutic antibodies. Results demonstrate that an antibody produced using the Sindbis virus vector system is able to protect mice against a lethal infection of the central nervous system (see column 15 lines 66-67 and column 16 lines 1-8 in particular).

Claim 80 is included because antibody is antibody irrespective of how it's made.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* recombinantly, chimeric, humanized or human taught by the `712 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the recombinant antibody offers great advantages with respect to post-translational modifications, stability, immunogenicity, and yields as taught by the `712 patent. Further, chimeric, humanized are human antibodies can be useful for the as therapeutic antibodies as taught by the `712 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/24/05 have been fully considered, but have not been found convincing.

Applicant argues that the antibodies described in Huang do not "specifically bind" to the open conformation. However, the term "specifically binds" does not preclude the reference antibody because Huang et al antibodies still "specifically binds" to the open conformation as evidenced by Lu et al. Further, Applicant's own specification discloses that those antibodies specifically bind to the open conformation (see table 3 in particular) as defined by applicant.

Regarding claim 26, applicant submits that these antibodies, indisputable also bind to a modified I-domain that is locked in the closed conformation by the L289C/K294C mutation. Applicant further argues that activation specific epitopes are absent from I-domains locked in the closed conformation. Applicant submits that antibodies that bind to an I-domain in the closed conformation necessarily do not bind to an activation specific epitope because the antibodies in Huang bind to a modified I-domain that is locked in the closed conformation, they do not bind to an activation specific epitope.

However, these antibodies bind the open conformation and therefore meet the claims limitations as is evidenced by Lu et al (also see the instant specification tables 2-3 in particular). Regarding Applicant argument that the referenced antibody binds the I-domain in the closed conformation, and that they do not bind an activation specific epitope, the Examiner disagree with that statement because the referenced antibodies do bind the open conformation i.e., an activation specific epitope.

16. Claims 114-117 and 122-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6, in view of U.S. Patent No. 5,843,712 and further in view of U.S. Patent No. 6,572,856.

The teachings of Huang *et al,* the '712 patent and Lu *et al* and the specification both cited as an evidentiary reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the antibody further comprising a physically linked detectable substance in claim 114, wherein the physically linked detectable substance comprises and enzyme, a fluorescenct material, or a radioactive material in claims 115-116, or the antibody further comprising a therapeutic moiety in claims 117-121, wherein the therapeutic moiety comprises a cytotoxin in claim 122, a

chemical therapeutic agent in claim 124, a protein possessing a desired biological activity in claim 125, a toxin in claim 126.

The `856 patent teaches monoclonal antibodies immunospecific for C3b(i) are conjugated to a therapeutic moiety such as a chemotherapeutic cytotoxin, e.g., a cytostatic or cytocidal agent (e.g., paclitaxol, cytochalasin B or diphtheria toxin), a thrombotic or anti-angiogenic agent or a radioactive label. In another embodiment, monoclonal antibodies immunospecific for C3b(i) are conjugated to a detectable substrate such as, e.g., an enzyme, fluorescent marker, luminescent material, bioluminescent material, or radioactive material (see col. 8 lines 45 to col. 9, line 8 in particular). Further, an antibody or fragment thereof can be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide. Therapeutic agents include antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), (e.g., vincristine and vinblastine). (see column 28, lines 15-38 in particular) the `856 patent teaches that the drug moiety can be a protein or polypeptide possessing a desired biological activity such as toxin (see col., 28, lines 51-55). The `856 patent further teaches that the anti-C3b(i) antibodies or fragments thereof are conjugated to a diagnostic or therapeutic agent can bed used diagnostically as a part of a clinical testing procedure to determine the efficacy of a given treatment regimen (see col., 27, lines 57-61 in particular). Finally, the `856 patent teaches that the antibodies specific for C3b(i) can be utilized to target tumor cells for the delivery of therapeutic or diagnostic agents, including cytotoxic, chemotherapeutic, immune-enhancing drugs, radioactive compounds, genetic material and immune effector cells (see col., 45, lines 1-5 in particular)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the recombinant antibodies and fragments thereof, which specifically bind to an integrin I-domain taught by Huang e*t a* in view of the `712 patent with a physically linked detectable substance, wherein the physically linked detectable substance comprises and enzyme, a fluorescenct material, or a radioactive material, or a therapeutic moiety, wherein the therapeutic moiety comprises a cytotoxin, a chemical therapeutic agent, a protein possessing a desired biological activity, a toxin taught by the `856 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such antibodies or fragments thereof which are conjugated to a diagnostic or therapeutic agent can bed used diagnostically as a part of a clinical testing procedure to determine the efficacy of a given treatment regimen. Further, such conjugated antibodies can be utilized to target tumor cells for the delivery of therapeutic or diagnostic agents, including cytotoxic, chemotherapeutic, immune-enhancing drugs, radioactive compounds, genetic material and immune effector cells as taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 127-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) and the specification on page 76, lines 7-8 and page 77, Table 6 in view of U.S. Patent No. 5,843,712 as applied to claims 25, 30, 74, 76-80 and 110, 112-113 above, and further in view of U.S Patent No. 6,413,963.

The teachings of Huang *et al*, Lu *et al* and the specification both cited as an evidentiary reference and the '712 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition and a pharmaceutically acceptable carrier in claims 127-130.

The '963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The '963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antibodies taught by Huang *et al* reference in a pharmaceutical compositions in a pharmaceutically acceptable carrier taught by the '963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by '963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Claims 84, 87-88 and 133-134 would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. 112, second paragraph, set forth in this Office action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
April 4, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600